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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,803	01/14/2004	James McSwiggen	MBHB03-465-C (400.142)	5421

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S. U.S.O.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference. The invention is further drawn to various modifications of the siNA, as well as to a pharmaceutical composition comprising the siNA molecule and a pharmaceutically acceptable carrier or diluent.

The claims encompass any double stranded siNA molecule that comprises a first nucleotide sequence with any amount of complementarity to any target RNA sequence, and a second sequence having any amount of complementarity to said first sequence,

wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference.

These are broad generic structural features, but applicants are not claiming this broad genus. Rather, applicants are claiming only the subset of this genus which is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference. Applicants have not described what defines this subset of exclusively siNA molecules that are chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference. The skilled artisan would not be able to envision the genus instantly claimed of those siNA molecules that are modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference without undue experimentation.

Applicant has not described a sufficient number of species of such modified siNA molecules to demonstrate what degree or type of modification actually results in said second sequence no longer being able to act as a guide sequence for mediating RNA interference. Applicant has not described a structure that would lead one of ordinary skill to construct only those that are modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference. The represent sequences provided are proof that applicant was in possession of some molecules, however, nothing about these sequences or applicant's specification tells us about the remainder of the claimed genus and whether they will direct cleavage or not.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the parent application of 10/693,059, which has an effective filing date of 10/23/2003. The instant case 10/757,803 does not receive the benefit of any of the other claimed priority documents because claims 1-17 of the instant case are not supported by the

specification and claims of the previously mentioned parent applications. Aside from 10/720,448 and 10/693,059, the parent applications do not disclose the language "...wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference" or support for such a statement. Thus, the instant application 10/757,803 is accorded an effective filing date of 10/23/2003.

Claims 1, 8, 9, 12, 13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference, wherein said siNA molecule comprises ribonucleotides. Each strand of the siNA duplex comprises about 19 to about 23 nucleotides, and each of the sequences comprise at least about 19 nucleotides that are complementary to the nucleotides of the other strand. Any pyrimidine nucleotides in the first or second sequence are 2'-deoxy-2'-fluoro pyrimidine nucleotides. The invention is further drawn to a pharmaceutical composition comprising the siNA molecule and a pharmaceutically acceptable carrier or diluent.

Parrish et al. teach modified double stranded siNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence, wherein said second nucleotide sequence is modified and at least 19 nucleotides are complementary between the first and second sequences. The siNA molecules taught by Parrish et al. comprise about 19 to about 23 nucleotides, more specifically 26 nucleotides. Parrish et al. teach siNA molecules comprising ribonucleotides. The siNA molecules taught by Parrish et al. meet the structural limitations of the instant claims, and therefore the second nucleotide sequence is considered to no longer act as a guide sequence for mediating RNA interference as instantly claimed. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the interference process (see summary). Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5). The assays taught by Parrish et al. comprise buffers (i.e. water) that are considered a pharmaceutically acceptable diluent. Therefore, the instant invention is anticipated by Parrish et al.

Claims 1, 7-11, 14, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (EMBO Journal, Vol. 20, No.23, pp. 6877-6888, 2001).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference, wherein said siNA molecule comprises ribonucleotides or does not comprise ribonucleotides. Each strand of the siNA duplex comprises about 19 to about 23 nucleotides, and each of the sequences comprise at least about 19 nucleotides that are complementary to the nucleotides of the other strand. Any pyrimidine nucleotides in said second sequence are 2'-O-methyl pyrimidine nucleotides, any purine nucleotides of the first or second strand are 2'-deoxy purine nucleotides, or any purine nucleotides in the first sequence are 2'-O-methyl purine nucleotides. The invention is further drawn to a pharmaceutical composition comprising the siNA molecule and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. teach 21nucleotide siRNA duplexes, wherein the antisense strand has complementarity to a target mRNA and the sense strand has complementarity to the antisense strand. 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach such duplexes to be modified in a manner that abolishes the ability of the second sequence to act as a guide sequence for mediating RNA interference. Elbashir et al. teach siRNA duplexes chemically modified to varying degrees, wherein the duplexes modified less than 100% comprise ribonucleotides and the duplexes modified 100% no longer comprise ribonucleotides. Elbashir et al. teach

complete substitution of one or both strands by 2'-deoxy residues or 2'-O-methyl residues, each resulting in abolished RNAi (see page 6882). The experiments taught by Elbashir et al. comprise buffers (i.e. water) that are considered to be pharmaceutically acceptable diluents (see materials and methods). Therefore, the instant invention is anticipated by Elbashir et al.

Claims 1-8 and 10-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Matulic-Adamic et al. (U.S. 5,998,203).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that said second sequence can no longer act as a guide sequence for mediating RNA interference, wherein said siNA molecule comprises ribonucleotides. The invention is further drawn to terminal modifications of the siNA duplex, as well as to a phosphorothioate linkage at the 3' end of the first sequence. The invention is drawn to a pharmaceutical composition comprising the siNA molecule and a pharmaceutically acceptable carrier or diluent.

The term "siNA" is defined in the instant specification, page 76, as referring to any nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, for example by mediating RNA interference or gene silencing in a sequence-specific manner. Matulic-Adamic et al. teach double stranded short

interfering nucleic acid molecules that comprise a first nucleotide sequence complementary to a target or a portion thereof, and a second sequence having complementarity to said first sequence. Matulic-Adamic et al. teach chemical modifications of the double stranded structure. The ribozymes taught by Matulic-Adamic et al. comprise ribonucleotides and cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Although Matulic-Adamic et al. are silent as to the role of the ribozyme in RNAi, the ribozyme meets all of the structural limitations of the instant claims and the second modified sequence would therefore be considered to no longer act as a guide sequence for mediating RNA interference as instantly claimed. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property.

For example, figure 3 contains a ribozyme structure that meets the structural limitations of the instant claims (see figure 3 and description of figure 3 in column 7). The structure encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. When 100% of the nucleotide positions are modified, the duplex is considered to comprise no ribonucleotides. The modifications can be in one or both of the strands. Helix 4 can be formed from two separate molecules, i.e. without a connecting loop. *In*

vitro RNA cleavage was carried out in reaction buffers containing water, which is a pharmaceutically acceptable diluent.

Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). Therefore, the ribozyme taught by Matulic-Adamic et al. meets the structural limitations of instant claims 1-8 and 10-17.

Double Patenting Rejection

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-17 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17 of copending Application No. 10/720,448. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The claims of the instant application and the claims of application '448 are identical.

Claims 1-17 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17 of copending Application No. 10/693,059. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The claims of the instant application and the claims of application '059 are identical.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:00 am – 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

JAMES SCHULTZ
PATENT EXAMINER